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FDA Regulation of Clinical Microbiology Diagnostic Devices

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The Food and Drug Administration (FDA) is charged with protecting the public health by ensuring the safety and efficacy of human and veterinary drugs, biological products, and medical devices. It is also charged with ensuring the safety of foods, cosmetics, and radiation-emitting products. More recently, the FDA has also been tasked with regulating tobacco products.

In regulating these products, the FDA strives to maintain a balance between the benefits of a specific product and the potential risks from its use. The FDA also has a role in helping to advance innovative products while ensuring that clinical evaluations are scientifically sound and that the public has access to accurate, science-based information (3).

Within the FDA, the responsibility for products used in patient diagnosis, treatment, and disease prevention is organized under the Center for Drug Evaluation and Research (CDER), the Center for Biologics, Evaluation, and Research (CBER), and the Center for Devices and Radiological Health (CDRH). Devices intended for use in the diagnosis of infectious diseases are reviewed by the Division of Microbiology Devices in the Office of *In Vitro* Diagnostic Device Evaluation and Safety (OIVD) within CDRH. The division is responsible not only for premarket evaluation but also for the postmarket monitoring of microbiology devices used to diagnose and/or mitigate disease. The division has no specific laboratory testing capability, and all reviews are conducted based on an evaluation of analytical (preclinical) and clinical data obtained from testing specimens obtained from intended-use populations and run in intended-use settings. It is worth noting here that retrovirus-specific diagnostic tests and all blood screening tests fall under the auspices of CBER review.

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There are several pathways to introduce diagnostic devices to the market. The two main paths are a premarket application (PMA), which can lead to approval of a diagnostic device, and premarket notification, which can lead to clearance of a device. The latter is widely known as a 510(k), named after the relevant section in the Federal Food, Drug and Cosmetic Act (here, the Act).

In the Act, the FDA was granted authority to regulate medical devices as specified in the medical device amendments of 1976 and the relevant regulations. *In vitro* diagnostic products, including microbiology devices, are devices under the Act and Title 21 of the Code of Federal Regulations (CFR). The Act divided the field of medical devices into either preamendment or postamendment devices, depending on when the devices were introduced into interstate commerce for commercial distribution. The foundation of any regulatory paradigm is the balance of measuring the risks against the benefits of using the device. The basic principle is to get safe and effective devices to market as quickly as possible while ensuring that devices on the market remain safe and effective. *In vitro* diagnostic devices (IVDs) are classified into class I, II, or III according to the risk to a patient of generating a false-positive or -negative result leading to misdiagnosis of the patient's condition from a particular device. This determines the level of regulatory control that is necessary to ensure safety and effectiveness. The classification of an IVD (or other medical device) determines the appropriate premarket review process (Table 1).

Class I includes devices for which any combination of general controls is sufficient to provide reasonable assurance of the safety and effectiveness of a device. General controls include, for example, prohibition against adulterated or misbranded devices. With the exception of "reserved medical devices" (e.g., microbiological specimen collection and transport devices [for a full list, see reference 6]), which would remain subject to premarket notification, the FDA has exempted almost all class I devices from the premarket notification and clearance requirements. However, these devices are subject to several limitations to their premarket notification exemptions, and if any of the limitations apply, then the device needs to be submitted to the agency (e.g., a device used to identify a recovered bacterial isolate from culture could be exempt while a device that detects the bacteria directly from a human specimen would be nonexempt). Another example is a device that has new technological characteristics that may raise new types of safety and effectiveness questions.

Class II devices are those which cannot be classified into class I because general controls alone may not be sufficient to provide reasonable assurance of the safety and effectiveness of such a device. In this situation, there is sufficient information to establish special controls to provide such assurance. Special controls include, for example, guidance documents issued by the FDA, availability of performance standards (specific guidance on the FDA's standards recognition process and on its use of standards may also be found on the FDA's website [7]), postmarket surveillance, patient registries, tracking requirement recommendations, and other appropriate actions.

The class III designation is for devices for which insufficient information exists to determine general and special controls that are sufficient to provide reasonable assurance of the safety and effectiveness of such devices. Examples include devices that are life-sustaining and/or life-supporting or tests where results present a risk of misdiagnosis that could cause serious

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TABLE 1. Types of FDA diagnostic device submissions based on a risk-based classification

Submission type[a]	Device class[b]	Comment	Example
Pre-IDE	NA[c]	A form of consultation submitted by the sponsor as a consultation (presubmission advice)	NA
None (exempt)	Exempt; it can be either a preamendment, class I, or class II device	Preamendment devices not significantly changed or modified, or class I/II devices specifically exempted by regulation	Biochemical identification panels, latex agglutination, or DNA probes for isolate identification
Premarket notification, 510(k)	I	Predicate device exists. General controls are usually sufficient. Most are exempt from submission, subject to limitations to the exemption[d]	A swab intended for the collection and transport of clinical specimens for the purpose of using the material for culture
	II	General controls do not provide reasonable assurance of safety. Special controls are needed	Antimicrobial susceptibility test systems
PMA	III	No predicate device; potential for unreasonable risk	Human papillomavirus or hepatitis B and C tests
De novo	III down-classified to II or I	Used for devices that have no predicate for which a combination of general and or special controls (such as a special controls guidance) can offer assurances of safety and effectiveness	Respiratory viral panel multiplex nucleic acid assay; norovirus assay
EUA	Dependent on disease and/or device	Defined in the Project BioShield Act of 2004; reserved for declared emergency. Subject to review by the agency, a medical device that has not been previously approved or cleared may be authorized to be used under specified conditions	2009 H1N1 influenza virus assays
IDE	Significant risk	Required for studies which involve managing the patient based on the result of the investigational device; an IDE is rarely needed for an *in vitro* device. Scientifically sound reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits	Influenza virus H5 clinical study; evaluation of rapid group B streptococcus test for use in delivery room
CLIA waiver	I, II, or III	At the time of clearance or approval, devices are CLIA-categorized into high- or moderate-complexity CLIA categories. Studies are defined in the CLIA waiver guidance document (16) to evaluate if a device qualifies to be considered for CLIA waiver	Rapid visual test strip for qualitative detection of group A streptococcal antigen in a throat swab; an HIV test using a buccal cavity swab and visual test strip

[a] PMA, premarket authorization; EUA, emergency use authorization; IDE, investigational device exemption; CLIA, Clinical Laboratory Improvement Amendments of 1988.
[b] Classes are determined according to risk, as follows: I, very low or low; II, medium; III, high.
[c] NA, not applicable.
[d] A microbiology *in vitro* device can be exempt from the premarket notification procedures subject to the limitations in 21 CFR 866.9. For example, a microbiology device used to identify a colony from culture might be exempt, but the same device will be subject to the limitation if the intended use is extended to include direct identification from clinical material.

injury and can lead to potential or unreasonable risk to patients and other individuals.

In vitro diagnostic products are a subset of medical devices. The Code of Federal Regulations (21 CFR 809.3) broadly defines *in vitro* diagnostic products as those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body (1).

Before discussing aspects relevant to microbiology device reviews, it is valuable to have a quick overview of the regulatory field that governs the evaluation of devices in general (including microbiological products) and the types of regulatory submissions that FDA receives for review. The limited scope of this article does not allow for extensive discussion; however, valuable information can be found in the FDA guidance document entitled "*In vitro* Diagnostic (IVD) Device Studies—Frequently Asked Questions" (8) and on the FDA website under the device advice section on device regulation and guidance (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm).

There are several elements that are considered in the evaluation of a new device. These include, but are not limited to, the intended use of the device, the population that has been tested, the location of testing, the reference methods used during the clinical evaluation, assay result interpretation, assay performance characteristics, assay technology, and whether the assay is for the determination of single or multiple analytes. All of the aforementioned elements are important, but it is worth noting that the level of FDA review and the type of studies requested are strongly influenced by the device's intended use claims and the risk associated with that use. The specimen type that can be tested and the setting where the specimen is obtained are also critical components of the intended use. As would be expected, new assays that rely on novel, not-well-established technology can be subject to a more stringent review process.

Based on the complexity of data and class of device submitted for FDA review, a team of subject matter experts is assembled that is comprised of FDA personnel with the technical, scientific, and regulatory knowledge to conduct a thorough review of submissions. External advisors and panel members are consulted whenever the need arises, and this can be in the form of either a formal panel meeting or homework assignment, in which opinion is sought from individual experts as

needed. For assays that require instrumentation, the review also includes evaluation of instrument hardware and software used to run the test and to interpret the results. Depending on the classification of the product under consideration, the microbiology division may also conduct a review of the quality system in place at the site of manufacture of the device and coordinate the conduct of inspections to help ensure that the products consistently meet applicable manufacturing requirements and specifications.

As shown in Table 1, there are several types of submissions. The pre-investigational device exemption (IDE) is a consultation in which sponsors seek advice from FDA regarding their study plans and regulatory pathway to market clearance/approval of their devices. Sponsors may use this form of communication with the FDA for any topic they wish to seek feedback on although this usually occurs at the preclinical evaluation stage of product development. A premarket notification, or 510(k), is usually submitted for a device for which there is a predicate (a device with similar intended use and/or technological characteristics). Although such devices seek a determination of substantial equivalence to a predicate device, comparative studies often require performance to be evaluated against a reference or gold standard. This is especially true for microbiology-related devices. Some devices are exempt from the requirement for a 510(k) either because they are preamendment devices or because they present low risks to health that can be mitigated by general or special controls. Demonstration of substantial equivalence can be assessed through adequate and well-controlled clinical evaluations. A premarket authorization, or PMA, is submitted for a class III test where the device itself and/or where the intended use is associated with the potential for unreasonable risk. Comparison to a predicate is not the way these devices are evaluated. Instead, they are evaluated by assessing the device's performance against clinical truth.

In some situations, an investigational device exemption can be considered, but the sponsor must demonstrate in the application that there is reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits to subjects and the importance of the knowledge to be gained. In addition, the investigation must be scientifically sound, and there should be reason to believe that the device, as proposed for use, will be effective.

An emergency use authorization (EUA) application is another type of submission, but this regulatory pathway is applicable only under special emergency circumstances. Section 564 permits the FDA Commissioner to authorize the introduction into interstate commerce of a drug, device, or biological product intended for use in an actual or potential emergency during the effective period of a declaration. EUA candidates include products and uses that are not approved, cleared, or licensed under sections 505, 510(k), and 515 of the Act or section 351 of the Public Health Service Act and where there is clearly an urgent need to have them available. The range of potential EUA products includes drugs such as antiviral and antibacterial agents, biological products such as vaccines, blood products, and biological therapeutics, and devices such as specific tests for diagnosis or blood screening and personal protective equipment (9).

DISCUSSION

Several discussion points were raised at the symposium based on the information exchanged. Increased communication between the FDA, clinical laboratories, and device manufacturers was emphasized. Several industry representatives spoke about their experiences. It was noted that the pre-IDE process was very valuable and that the exchange with the division of microbiology devices in OIVD has been productive. One area of discussion focused on ways in which the FDA could communicate to sponsors when a change in requirements and/or current thinking occurs. It was suggested that the agency consider ways of enhancing communication to assay developers and to the laboratory community who might be affected when there are changes in regulatory policy based, for example, on changes in medical practice or a new technology.

Relevant to that discussion, it was mentioned that the FDA regularly issues guidance in an effort to make the FDA submission and review process more consistent. Guidance documents are not rules but provide FDA's current thinking on a topic. Examples of guidance documents relevant to microbiology include guidance documents that cover the subjects of antimicrobial susceptibility test (AST) systems and molecular methods for detection of influenza virus and MRSA (10, 11, 12).

Another important communications tool is the database which contains all *in vitro* diagnostic products cleared or approved, including the 510(k) decision summaries and PMA summaries of safety and effectiveness. The database can be searched by 510(k) or PMA number, applicant, device name, or FDA product code (13). This database is updated monthly to add new decision summaries and therefore can be a valuable source of information on current submission expectations for a given device. These summaries outline the studies and the performance evaluation on which the decision to grant clearance or approval were based. Because of the rapid publication process (compared to the slower process of developing guidance documents), the discussants agreed that these databases provide direction to the scientific community, and it was recommended that the availability of this form of communication be highlighted and promoted.

Besides publishing guidance documents and decision summaries that are helpful scientific and regulatory tools, the FDA also officially recognizes a large number of written standards (more than 30 Clinical and Laboratory Standards Institute [CLSI] standards that specifically address microbiology and molecular microbiology testing are recognized). It is important that recognition can be full or partial, as specified. Conformance to recognized written standards (e.g., standards published by CLSI) is helpful to the manufacturer and to the FDA as this provides assurance regarding consistency of submissions and helps the agency in achieving uniformity of evaluation of a given device type (4). This provides for an easier and more uniform procedure that streamlines the process for both the FDA reviewer and the sponsor. Specific guidance on the FDA's standards recognition process and on its use of standards may also be found on the FDA's website and in its standards database (7).

There was some discussion of how the microbiology division in OIVD engages the scientific community to receive feedback

on various issues. The conveners discussed the role of the microbiology advisory panel. During this discussion, it was explained that the FDA microbiology advisory panel members are consulted whenever the need arises, and this can be in the form of either a panel meeting or a homework assignment, in which opinion is sought from individual experts as needed. In addition and as the need arises, FDA organizes workshops and meetings to consult experts on various topics. These meetings result in concept papers and summaries that provide future direction. For example, the FDA recently collaborated with the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA) in organizing public workshops that addressed respiratory tract infections and tuberculosis, and these workshops were also broadcast widely via the web. Proceedings from the IDSA-FDA workshop were published as a supplement in *Clinical Infectious Diseases* (2) and include an article which described FDA's perspective on diagnostic device clinical studies for respiratory tract infections (5). To expand awareness about future meetings, the conveners suggested that announcements be disseminated through the American Society for Microbiology (ASM) or Association of Public Health Laboratories (APHL) and other organizations to increase awareness of such events, especially for workshops/seminars/public hearings that may be readily available via webcast.

The advent of molecularly based assays for diagnosis of infectious agents and/or markers of antimicrobial resistance directly from clinical specimens has certainly presented prospects for rapid availability of results that might enhance patient care. This topic was discussed, and conveners agreed that these technological advances should be applied and adopted. There were some participants who advocated for replacement of existing methods with the more rapid and sophisticated assays. The discussants appreciated the fact that the field of infectious disease diagnosis is constantly changing and that there is a need to adapt to the newer technologies but also that there are situations that are more suited than others for such applications. In a similar way, the FDA is also faced with the parallel challenge of evaluating studies to bring forward complex and new device technologies that are changing the landscape of testing. Such changes in technology have resulted in the increased complexity of submissions, such as multiplex assays that analyze multiple pathogens and/or resistance markers. It is important to mention that in evaluating microbiology devices, comparisons can be made either to a well-established single reference method (e.g., culture) or to multiple results to evaluate clinical truth or true patient infection status (e.g., using two different molecular assays that measure two independent nucleic acid targets in evaluating an assay for detection of *Chlamydia trachomatis* from multiple clinical specimen types).

The issue of updating the antimicrobial susceptibility breakpoints and the impact of this on *in vitro* antimicrobial susceptibility test (AST) device manufacturers were of great interest. Participants suggested that there was an urgent need to address this key topic. In this discussion, it was noted that the current FDA process has been outlined in a guidance document which was published jointly by CDER and CDRH (14). This document outlines the steps needed for a drug application holder to update information in the antimicrobial drug label and provides directions to manufacturers of AST devices for updating labeling regarding susceptibility testing information. It is apparent that success and timely updates are dependent on and require cooperation and collaboration from multiple parties. This can have a positive impact for AST device manufacturers and the clinical microbiology laboratories.

The process for clearance/approval of diagnostic assays for rare diseases and in situations where the specimens are extremely valuable and/or difficult to obtain was addressed. An example was given of the challenges involved in evaluating a diagnostic assay for herpes simplex virus from cerebrospinal fluid. It was mentioned that during early collaboration between the sponsor and the FDA (e.g., through the pre-IDE process), it may be possible to outline studies in which a combination of prospective, retrospective, and/or spiked specimens may be used to investigate and establish assay performance. However, it was acknowledged that this is highly dependent on multiple factors, such as disease, organism, target detected, assay, technology, and availability of a well-established reference assay.

A topic of importance to many participants was how the FDA evaluates a device's postmarket performance after initial clearance or approval. It was noted that PMA devices are subject to stringent postmarketing requirements, but those same requirements do not apply to 510(k) devices. However, all devices are subject to the medical device reporting system through which the FDA monitors device performance in the field. This process is outlined in the guidance document "Medical Device Reporting for User Facilities" (15). It is through this system that end users can, and should be, encouraged to report issues they face with performance of a given device.

In conclusion, the conveners agreed on several proposals in order to foster a better understanding of regulatory and scientific issues and to advance the field of diagnostic clinical microbiology devices; it was proposed that the FDA, industry, and the clinical microbiology community should do the following:

1. Schedule recurrent, joint roundtable meetings to discuss relevant issues of common concern. Workshops to be held in conjunction with ASM or Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meetings would seem to be particularly valuable since there is a good chance that representatives from all parties would be available.
2. Enhance awareness, through ASM publications, internet communications, or other means, of the importance of medical device reporting aspects by the end users.
3. Enhance dissemination of information on FDA workshops/webcasts that are pertinent to the clinical microbiology community.
4. Enhance the process by which the professional community can address device specific issues with the FDA.
5. Establish biobanks/repositories of well-defined clinical specimens that may be useful in facilitating evaluation of devices, particularly for rare diseases or for cases where obtaining specimens may be difficult.
6. Enhance cooperation between FDA, industry, standard-setting organizations, and clinical laboratories on AST breakpoint issues.

Session discussants: Sheldon Campbell, Daniel Diekema, Richard Hodinka, Robert Jerris, Sue Kehl, Markus Kostrzewa, Michael Loef-

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